

Early Cutaneous Lesions Secondary to Hydroxyurea Therapy

Franca Radaelli,* Rossella Calori, Paola Faccini, and Anna Teresa Maiolo

Servizio di Ematologia, Istituto di Scienze Mediche, Università di Milano, Ospedale Maggiore, I.R.C.C.S., Milan, Italy

Hydroxyurea is a usually well-tolerated cytostatic agent, but its side effects include cutaneous lesions that appear after several years of maintenance therapy with hydroxyurea. The reported incidence of such adverse reactions varies from 10 to 35%; in our Center it is 2%. We describe a patient with essential thrombocythemia who presented with ulcers of the hands only 15 days after hydroxyurea treatment. *Am. J. Hematol.* 58:82–83, 1998. © 1998 Wiley-Liss, Inc.

Key words: hydroxyurea; essential thrombocythemia; skin lesions

CASE REPORT

A 65-year-old man with essential thrombocythemia was referred to our Hematological Department in September 1996 with a 4-month history of skin lesions on the dorsa of his hands. His past medical history included an acute myocardial infarction (May 1991). In May 1992, essential thrombocythemia was diagnosed according to the criteria established by the Polycythemia Vera Study Group [1]. The patient was treated intermittently with pipobroman for the following 4 years. In April 1996, the patient developed refractory thrombocytosis and was switched to hydroxyurea. After 15 days of treatment, a lichen planus-like dermatitis appeared on the dorsa of the hands, which progressively worsened to ulcers over the following months. The patient was admitted to the Dermatological Department of our hospital on August 24, 1996, and histopathological examination of a skin biopsy documented polymorphonuclear infiltrate in the papillary and reticular dermis, with dilatation of the dermal vessels. Antiskin antibodies determined by indirect immunofluorescence and antinuclear antibodies were negative.

On September 3, 1996, the patient received oral glucocorticoids but there was no significant improvement in the lesions. On September 11, he was referred to our Institution because of thrombocytosis refractory to hydroxyurea (platelets $1,390 \times 10^9/L$), anemia (hemoglobin 10.2 g/dl), and leucopenia (white blood cells $2.6 \times 10^9/L$) (Fig. 1). Hydroxyurea was immediately withdrawn because we thought it could be responsible for both the myelosuppression and the skin lesions.

One week later, we observed a clear improvement in

the skin ulcers, and an improvement in blood cell counts. As the patient developed thrombophlebitis in the right leg, and since he had a history of myocardial infarction, therapy with busulfan and calciparine was started. The glucocorticoids were progressively tapered but the concurrent treatments were continued.

Over the following 4 months, a slow but progressive improvement in the skin lesions led to the healing of the ulcers, and good clinical and hematological control was obtained.

DISCUSSION

Hydroxyurea is a cytostatic agent that has been widely used for the treatment of myeloproliferative diseases. Its mechanism of action is not yet fully understood.

The major adverse reactions are reversible and dose-dependent marrow suppression, megaloblastosis, and gastroenteric disturbances. Other adverse reactions are dermatological alterations: alopecia [2], xerosis [2–6], skin hyperpigmentation [2,4], ungual hyperpigmentation [4,5], keratotic lesions [4,6–8], erythematous scaling eruptions [2,4], dermatomyositis-like dermatitis [4,7], and lichen planus-like dermatitis [2]. These lesions are

*Correspondence to: Franca Radaelli, MD, Servizio di Ematologia Diagnostica, Ospedale Maggiore, Via Francesco Sforza 35, 20122 Milano, Italy.

Received for publication 3 November 1997; Accepted 12 November 1997



Fig. 1. Skin lesions at our first observation.

mainly localized to the extremities and can evolve into ulcers [2,4,5,7] or lead to an atrophic outcome [2,5]. An association between hydroxyurea therapy and multiple skin carcinomas on light-exposed areas has been reported in only one case [6].

Most of the cutaneous side effects of hydroxyurea occur during long-term therapy, with the first lesions usually being observed after 0.7 to 7 years. The clinical feature of our case is the early appearance of skin lesions, only 15 days after the start of hydroxyurea therapy. These lesions markedly worsened during the course of the therapy, but rapidly improved as soon as the drug was withdrawn. We assume that these lesions represented a side effect of hydroxyurea treatment because there was no chronological relationship between the appearance, worsening, and regression of the lesions and either the complementary therapy received by the patient or the control of the hematological disease.

In our patients with essential thrombocythemia, the rate of major skin lesions during long-term hydroxyurea therapy is about 2% (2/101 patients), and seems to be less frequent than that reported in the literature (10–35%) [2]. Sigal et al. [4] did not withdraw hydroxyurea therapy from a patient with skin ulcers, and Kennedy et al. [2] proposed an intermittent-dosage regimen. However, we think that the appearance of severe skin lesions requires hydroxyurea withdrawal, particularly because alternative cytostatic drugs can be used. Furthermore, in the case reported here, the patient not only presented a moderate functional disturbance of the hands, but also severe esthetic and, consequently, psychological discomfort. In the other case that we have observed, a malleolar ulcer led to difficult ambulation.

It is interesting to note that the rate of skin manifes-

tations seems to be related to the underlying disease. Kennedy et al. [2] reported skin hyperpigmentation in 3/20 patients with chronic myeloid leukemia (15%), and Dahl et al. [9] noted a higher rate of 44% in patients with psoriasis; Sharon et al. [10] did not report a single case of cutaneous lesions in 36 patients with polycythemia vera. Further studies of larger samples are necessary to determine the real incidence of minor and major skin lesions due to hydroxyurea.

REFERENCES

1. Murphy S, Iland H, Rosenthal D, Laszlo J: Essential thrombocythemia: An interim report from Polycythemia Vera Study Group. *Semin Hematol* 23:177–182, 1986.
2. Kennedy BJ, Smith LR, Goltz RW: Skin changes secondary to hydroxyurea therapy. *Arch Dermatol* 111:183–187, 1975.
3. Senet P, Aractingi S, Porneuf M, et al: Hydroxyurea-induced dermatomyositis-like eruption. *Br J Dermatol* 133:455–459, 1995.
4. Sigal M, Crickx B, Blanchet P, et al.: Lésions cutanées induites par l'utilisation au long cours de l'hydroxyurée. *Ann Dermatol Veneréol* 111:895–900, 1984.
5. Thomas L, Ferrier E, Moulin G: Dermatomyositis-like eruption complicating hydroxyurea therapy of chronic myelogenous leukemia. Report of a case and literature review. *Eur J Dermatol* 2:492–495, 1992.
6. Papi M, Didona B, De Pittà O, et al: Multiple skin tumors on light-exposed areas during long-term treatment with hydroxyurea. *J Am Acad Dermatol* 28:485–486, 1993.
7. Richard M, Truchelet F, Friedel J, et al: Skin lesions simulating chronic dermatomyositis during long-term hydroxyurea therapy. *J Am Acad Dermatol* 21:797–799, 1989.
8. Stasi R, Cantonetti M, Abruzzese E, et al: Multiple skin tumors in long-term treatment with hydroxyurea. *Eur J Haematol* 48:121–122, 1992.
9. Dahl MGC, Comaish JS: Long-term effects of hydroxyurea in psoriasis. *Br Med J* 4:585–587, 1972.
10. Sharon R, Tatarsky I, Ben-Arieh Y: Treatment of polycythemia vera with hydroxyurea. *Cancer* 57:718–720, 1986.